

Vesicoureteral Reflux

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ABSTRACT

Vesicoureteral reflux (VUR), the retrograde flow of urine from the bladder toward the kidney, is common in young children. About 30% of children with urinary tract infections will be diagnosed with VUR after a voiding cystourethrogram. For most, VUR will resolve spontaneously; 20% to 30% will have further infections, but few will experience long-term renal sequelae. Developmentally, VUR arises from disruption of complex signaling pathways and cellular differentiation. These mechanisms are probably genetically programmed but may be influenced by environmental exposures. Phenotypic expression of VUR is variable, ranging from asymptomatic forms to severe renal parenchymal disease and end-stage disease. VUR is often familial but is genetically heterogeneous with variability in mode of inheritance and in which gene, or the number of genes, that are involved. Numerous genetic studies that explore associations with VUR are available. The relative utility of these for understanding the genetics of VUR is often limited because of small sample size, poor methodology, and a diverse spectrum of patients. Much, if not all, of the renal parenchymal damage associated with end-stage disease is likely to be congenital, which limits the opportunity for intervention to familial cases where risk prediction may be available. Management of children with VUR remains controversial because there is no strong supportive evidence that prophylactic antibiotics or surgical intervention improve outcomes. Furthermore, well-designed genetic epidemiological studies focusing on the severe end of the VUR phenotype may help define the causal pathway and identify modifiable or disease predictive factors.

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DEFINITIONS

Vesicoureteral reflux (VUR) is the retrograde flow of urine from the bladder into the ureter and toward the kidney secondary to a dysfunctional vesicoureteric junction. This junction usually acts like a one-way valve, allowing urine flow from the ureter into the bladder and closing during micturition, preventing back flow.¹ Effective valve function is dependent on the coordinated action of several factors. These include the length of the submucosal ureter,² the width of the ureteric opening,³ the muscles of the trigone

and ureter,⁴ and coordinated ureteric peristalsis.⁵ VUR is detected most commonly during voiding, when intravesical pressure rises, but may occur any time in the voiding cycle, particularly when bladder function is abnormal.^{6,7} Severity is graded using the International Reflux Study system, which includes domains such as height of retrograde flow and dilation and tortuosity of the ureters (Figure 1).⁸ Five categories are possible, grade V being most severe, and intrarenal VUR is recorded separately. The reference standard test for VUR is voiding cystourethrogram (VCUG), which has

excellent interreader reliability in the setting of childhood urinary tract infection.⁹

PREVALENCE

VUR is common in childhood, but precise prevalence is uncertain because large-scale population screening using VCUG has not been done and cannot be justified. Studies of the frequency of VUR have examined small groups of “well” children, newborns with antenatal renal tract dilation, children after UTI and siblings of affected children or families with some indication of urinary tract problems.

Most review articles suggest a frequency of around 1% in well children,^{10–12} but primary studies are more heterogeneous. Table 1 summarizes the methods and results of primary studies designed to determine the frequency of VUR in well children. Fifteen studies have been performed with sample sizes varying from 10 to 722 (average 119). None of the 15 studies used the same cystography method, and each method is likely to have differing test performance (sensitivity and specificity). Reported frequencies of VUR varied from 0% to 30% and the age range was large, suggest-

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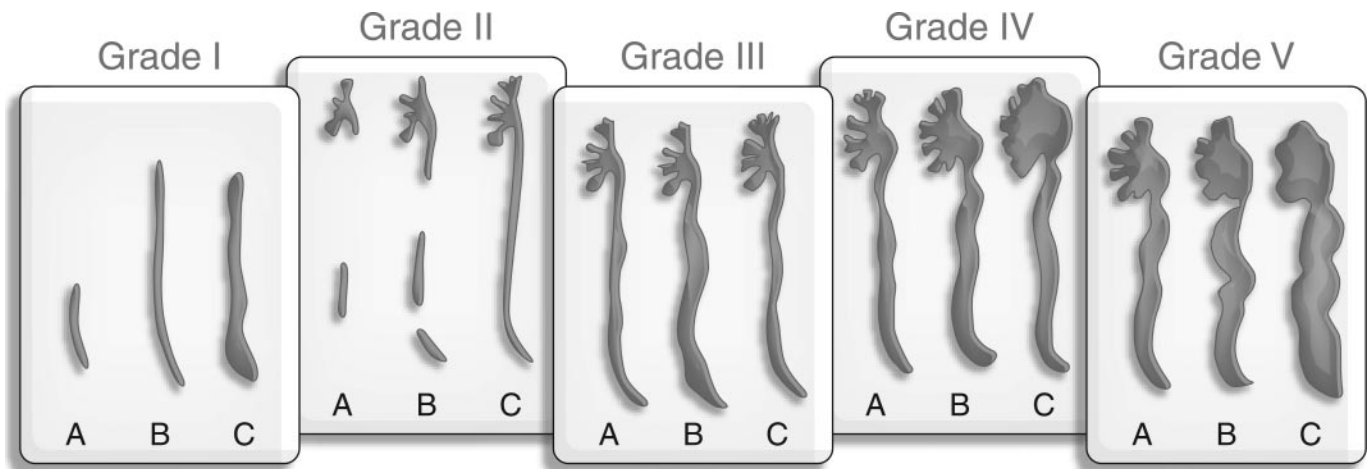


Figure 1. International Reflux Study grading system. (Reprinted with permission from Lebowitz *et al.*,⁸ *Pediatric Radiology*, Springer Verlag.)

ing very different study populations. This is important because VUR is known to spontaneously resolve with age. These studies show that estimates of VUR frequency in well children are imprecise but may be higher than the usual quoted figure of 1%. Study design is crucial to the estimate of frequency and data from studies that do not utilize the reference

standard on all participants will include error.

Since the 1980s many studies have examined newborn infants with renal tract dilation on antenatal ultrasound. Depending upon the threshold used, commonly ≥ 4 mm,¹³ 0.2% to 9.6% of newborn infants have dilation and of these 3% to 19% had VUR diagnosed

by VCUG.^{14–19} This translates to between 0.006% and 1.8% of the newborn population having VUR. However, extrapolating from these data is problematic because it assumes that dilation is always present with VUR and that ultrasound detects all dilation (*i.e.*, 100% sensitivity). If ultrasound sensitivity were as low as 30%, as it is in

Table 1. Characteristics of studies used to determine the prevalence of vesicoureteral reflux in children without a predisposing condition

Year	N	Age (yr)	Cystography Methods		Prevalence of VUR, % (95% CI) ^a	Reference
			Contrast Medium	Frequency of Imaging in Relation to Voiding		
1916	10	3 to 10	20% Cargentos emulsion of silver iodide 10% thorium nitrate	Single-multiple, nonvoiding	30.0 (10.81 to 60.3)	103
1949	43	0 to 12	4% Sodium iodide	Single nonvoiding	4.7 (3.2 to 15.5)	104
1951	722	— ^b	— ^b	Pre- and postvoid no voiding images	0 (0 to 0.5)	105
1954	24	1 to 74	Skiodan	0, 30, 60 min after instillation, no voiding images	0 (0 to 13.8)	106
1955	50	0 to 0.5	Ioduron 20%	Fluoroscopy, multiple, nonvoiding	2.0 (0.4 to 10.5)	107
1957	101	0 to 13	— ^b	Multiple pre- and postvoiding	0 (0 to 3.7)	108
1958	100	0 to 14	10% Sodium iodide	Single pre- and postvoid	1.0 (0.2 to 5.4)	109
1958	445	3 to 15	Barium sulphate	Multiple voiding	13.7 (10.5 to 16.9)	110
1960	50	—	Skiodan	Single pre- and postvoiding	0 (0 to 7.1)	111
1964	26	<2 d	— ^b	Fluoroscopy, pre- and postvoiding	0 (0 to 12.9)	112
1967	102	0 to 5	Urographine 76% and sodium chloride 0.9% 1:1	Single voiding image	28.2 (20.6 to 37.8)	113
1967	66	<1	— ^b	— ^b	0 (0 to 5.5)	114
1975	28	<1	— ^b	Incidental fetal, nonvoiding	3.6 (0.6 to 17.7)	115
1981	45	0 to 1	— ^b	Single voiding	8.9 (3.5 to 20.7)	116

^aVUR, vesicoureteral reflux.

^bDenotes details not provided

Table 2. Molecules studied in knockout animal models that appear to be involved in ureteric bud formation and growth^a

Name	Acronym ^b	Human Gene Chromosomal Location	Knockout Mouse Renal Phenotype	Reference
Transcription factors				
empty spiracles homolog 2	<i>emx2</i>	10q26.1	Bilateral agenesis	117
eyes absent1 homolog	<i>eya1</i>	8q13.3	Bilateral agenesis, hypoplasia	118,119
Forkhead box C1	<i>foxc1</i>	6p25	Ureteral anomalies	120
Forkhead box C2	<i>foxc2</i>	16q22-24	Ureteral anomalies	120
glutamyl-tRNA amidotransferase subunit 2 binding protein 3	<i>gata-3</i>	10p15	Wolffian duct elongation, deformities in ducts and epithelial positioning (lethal)	121
homeobox A11	<i>hoxa11</i>	7p14-15	Agenesis, hypoplasia	122
homeobox D11	<i>hoxa11</i>	7p14-15	Agenesis, hypoplasia	122
LIM homeobox 1 gene (forming proteins)	<i>lhx1 (lim1)</i>	17q12	Bilateral agenesis	123
paired box	<i>pax-2</i>	10q26	Bilateral agenesis (−/−), hypoplasia (−/+)	124
roundabout, axon guidance homolog 2	<i>robo2</i>	3p12.3	Supernumery ureteric buds + other abnormalities	125
Sal-like 1	<i>sall1</i>	16p12.1	Agenesis	126
SLIT homolog 2	<i>slit2</i>	4p15.2	Supernumery ureteric buds + other abnormalities	126
Wilms tumor gene 1 transcription factor 21	<i>wt1</i>	11p13	Bilateral agenesis	127
	<i>tcf2 (pod1)</i>	6pter-qter	Agenesis	128
Growth factors				
bone morphogenetic protein 4	<i>bmp4</i>	14q22-23	Lethal (−/−); duplicated system, cystic kidneys, hydronephrosis (−/+)	129
bone morphogenetic protein 7	<i>bmp7</i>	20q13	Dysplasia, hydroureter	130
fibroblast growth factor 10	<i>fgf10</i>	5p12-13	Hypoplasia, dysplasia	131
fibroblast growth factor receptor 2	<i>fgfr2</i>	10q26	Agenesis	132
growth differentiation factor 11	<i>gdf11</i>	12q13.2	Agenesis	133
glial cell line-derived neurotrophic factor	<i>gdnf</i>	5p13.1-p12	Bilateral agenesis(−/−), severe	134
glial cell line-derived neurotrophic factor family receptor α 1	<i>gfra1</i>	10q26	Agenesis, dysplasia	135
receptor tyrosine kinase proto-oncogene	<i>ret</i>	10q11.2	Agenesis, dysplasia (−/−)	136
			VUR (with over expression)	137
Others				
activin A type II receptor B	<i>acvr2b</i>	3p22	Agenesis, hypoplasia	138
angiotensin type 2 receptor 1	<i>agtr1</i>	3q21-q25	Hypoplasia/dysplasia, ureteral anomalies, CAKUT	50,139
cytochrome c oxidase subunit II	<i>cox2</i>	Mitochondrion	Dysplasia	140
glypican 3	<i>gpc3</i>	Xq26.1	Dysplasia, hydroureter	141
heparan sulfate 2-O-sulfotransferase	<i>hs2st</i>	1p31.1-p22.1	Bilateral agenesis	142
integrin α M	<i>itgam</i>	16p11.2	Bilateral agenesis	143
Kruppel-like factor 6	<i>klf-6</i>	10p15	—	144
retinoic acid receptor α	<i>rara</i>	17q21	Agenesis, dysplasia	145,146
retinoic acid receptor β	<i>rarb</i>	3p24	Agenesis, dysplasia	145,146
uroplakin II	<i>upk2</i>	11q23	Hydronephrosis, VUR	147
uroplakin IIIa	<i>upk3a</i>	22q13.31	Dysplasia, VUR, renal failure	148

^aMolecules are defined based on their signaling and regulatory factors, chromosomal location and proposed affect on mouse kidney development. −/− refers to homozygous null (*i.e.*, both alleles nonfunctional); −/+ heterozygous (*i.e.*, one nonfunctional allele); CAKUT, congenital abnormalities of the kidney and ureteric tract; LIM, limb deformity; SLIT, suppressor of lineage; Sal, salivary. ^bHUGO Human Genome nomenclature (if mouse nomenclature differs, appears in brackets).

children after UTI, then studies would suggest a frequency of VUR of between 0.2% and 6%.

There are numerous case series of children with UTI who underwent VCUG, and consistently 25% to 40% of these children have VUR.^{20–24} Because the cumulative incidence of UTI in children is around 6%,²⁵ we can calculate that between 1.5% and 2.4% of all children will be diagnosed with VUR after a UTI. Again, this is probably a low estimate given that not all children with VUR develop a UTI.

Another group of children investigated for VUR are those with a family history of VUR or reflux nephropathy. A review of 10 primary studies of siblings with VUR²⁶ demonstrates large variability in reported frequency of VUR; 11% to 67%. In many of these primary studies, verification of VUR in older family members was incomplete or problematic.^{27,28} It is therefore difficult to estimate with certainty the probability of VUR in family members of index cases.

Studies reporting the frequency of VUR give inconsistent results. Much of the variation can be attributed to study design, particularly the differences in diagnosing VUR, selection bias, and recall bias. The true prevalence of VUR in children remains uncertain: 1% is probably conservative, and 10% to 20% may be possible, suggesting VUR is largely asymptomatic

CLINICAL SPECTRUM

VUR can be an isolated finding and called primary reflux, or associated with urological abnormalities such as posterior urethral valves or ureterocele and referred to as secondary reflux.^{29–32} VUR can also occur as part of multiorgan malformation syndromes.^{33–36} The finding of collections of abnormalities of kidney and ureteric development has led to the term congenital abnormalities of the kidney and ureteric tract (CAKUT).^{37,38} In CAKUT, VUR is the most common abnormality among other disorders such as duplex systems, obstruction, dysplasia,

and single kidneys. This suggests the developmental processes that have gone awry in these syndromes have many phenotypic effects.

Although most well-designed prospective studies are small, follow-up analyses of children with primary VUR suggests that most do well. In a study of children with moderate to severe VUR (grades III to V), 55% of children showed resolution of VUR at 16 mo of age.³⁹ A 10- to 41-yr follow-up study of 226 children with VUR and UTI, reported resolution of VUR in 69%.⁴⁰ The morbidity reported in this study was also small with only 15 of 226 (6.6%) children being hypertensive at follow-up. Severe renal scarring identified at initial UTI was the primary predictor of hypertension in 14 of 15 (93%) children. In most follow-up studies VUR is a poor predictor of renal damage and hypertension.^{41,42}

ETIOLOGY OF VUR

Developmental Aspects

Formation of the ureter and kidney begins at day 35 of human gestation with emergence of the ureteric bud from the base of the Wollfian duct above the urogenital sinus (primitive bladder). As the ureteric bud grows toward the metanephric mesoderm (primitive kidney), reciprocal signals between the structures induce differentiation. During maturation of the ureters, evidence suggests programmed cell death (apoptosis) is involved in directing insertion of the ureters into the bladder.⁴³ Many signaling molecules and receptors involved in kidney development have been studied using knockout animal models⁴⁴ and are summarized in Table 2.

Historically there were two views on the development of renal parenchymal abnormalities and VUR. The first suggests that VUR arises from physical stresses resulting from obstruction and dysfunction of the bladder and vesicoureteral junction.⁴⁵ Studies have shown that induced obstruction in animal fetuses results in renal parenchymal abnormality, but presence of VUR was not determined.^{46,47} The second

theory proposes that abnormal ureteric budding and/or dysfunctional interactions between the ureteric bud and metanephric mesenchyme give rise to VUR and other renal abnormalities⁴⁸. Mouse embryo studies^{38,49,50} demonstrate that abnormal ureteric budding was evident in many of the mice that developed renal tract anomalies. Investigators propose that abnormal budding explains the occurrence of VUR. Mackie and Stephens suggest that when ureteral budding occurs at an ectopic site the ureteral orifice will also be ectopic, leading to a defective ureterovesical valve and VUR phenotype.⁴⁸ The studies on apoptosis by Batourina *et al.* demonstrate a mechanism by which insertion of the ureter into the bladder can be perturbed and muscular control of these openings *via* the trigone may be altered.^{43,51} To date no human studies have shown VUR together with dysregulation of this process. Direction of urine flow is also influenced by the muscles of the trigone and ureter and peristalsis of the ureter. Interstitial cells of Cajal are thought to be responsible for pacemaker activities in the ureter.^{52,53} Interstitial cells of Cajal are linked to each other by gap junctions that allow intercellular signaling. Decreased numbers of interstitial cells of Cajal has been associated with various motility disorders,^{54,55} and a recent study suggests that children with VUR may have reduced numbers of these cells and a decrease in gap junctions.⁵⁶

Although several mechanisms have been proposed to explain pathogenesis of VUR, little evidence exists in humans to confirm these theories. Existing studies show that VUR can be a congenital variant resulting from altered development. Few of the signaling molecules identified in animal models have been studied in people. Some exceptions include uroplakin IIIa, and conflicting findings are demonstrated.^{57,58}

Familial VUR

Many groups have studied VUR in the context of a familial disorder because sibling recurrence, parent-child transmission, and twin concordance (monozygotic 80% to 100%, dizygotic 35% to 40%)⁵⁹ provide good evidence for heritability.^{60–65} Assign-

ing etiological fractions to familial compared with sporadic cases of VUR is difficult because assigning a phenotype to older asymptomatic family members is problematic; testing is inappropriate, it may misclassify past VUR, and absence of clinical history may indicate asymptomatic VUR or no VUR.

The majority of reported pedigrees have shown dominant inheritance patterns,^{66–70} but cases of recessive⁶⁸ and X-linked inheritance are also reported.^{71,72} Thus familial VUR appears variable in its mode of inheritance. In the linkage study by Feather *et al.*, seven families displaying dominant inheritance of VUR were included in the analyses; five of the seven showed linkage to chromosome 1 and two families did not.⁷³ Feather *et al.* concluded that the VUR phenotype may result from an alteration in a number of different genes on different chromosomes.⁷³ Early family segregation studies suggested that more than one genetic alteration may be responsible for VUR in some families^{74,75} It appears that in some families VUR can result from one DNA change, whereas in others more than one DNA change is required. Given the genetic variability, phenotypic variability is not surprising. Genetic factors may also be influenced by environmental exposures, leading to differing phenotypes despite identical gene changes. Evidence to support the heritability of VUR is strong, yet it cannot be assumed that the mode of transmission, the number of specific mutations, or expressed phenotype will be the same across different families.

Genetic Association Studies

Assuming that alterations to ureteral budding, placement of the ureters, and cellular differentiation are mechanisms that can lead to VUR, the number of candidate molecules available for study is vast. Absence, altered amounts, changes in functionality, or temporal changes in expression of any of these molecules may result in changes to normal kidney and urinary tract development. Davies has compiled a web-based database listing possible candidate genes involved in kidney development.⁷⁶ An enormous litera-

ture base exists that aims to identify which chromosome or genes are associated with phenotypes that include VUR. These studies, many of which have limited applicability to primary VUR, are useful in generating hypotheses for further exploration. Table 3 lists some of these studies and demonstrates the diversity of phenotypes that can include VUR.

A number of studies that use candidate regions/genes and test the hypothesis of an association with VUR are listed in Table 4. Although few studies specify their assumptions, study design suggests that an absolute association is hypothesized. Some studies show conflicting findings, and this is probably a result of study design differences. Sample sizes are generally too small to identify small influences on phenotype,⁷⁷ and combinations of genotypes are rarely considered. Reports of positive associations may reflect type I error or confounding for alternative associations. Studies reporting an association between VUR and HLA type and ABO blood groups may represent an association with immune response to infection, or linkage with another site. Abnormalities in the angiotensin-converting enzyme insertion/deletion site are frequently studied but inconclusive. Positive association may indicate linkage to another site, whereas failure to identify an association does not rule out other sites within the gene or regulatory regions of the gene. The remaining VUR association studies explore a multitude of DNA sites/genes across the whole spectrum of VUR, but they are largely uninformative. Given the diversity of phenotype for VUR, clustering studies by phenotype of participants brings together those with more similar disease and thus greater likelihood of similar cause. Careful consideration of linkage disequilibrium is also required.

Measurement error in genotyping is also of concern and details of methodology are important. A report on the appraisal of 40 studies using molecular technology demonstrated limitations on repeatability and absence of blind-

ing for interpretation of genotyping.⁷⁸ Visual inspection is required for many methods, thus observer variability is possible. In the compiled list of VUR studies, the more recent papers documented methodology to some extent but efforts to limit error (*e.g.*, blinded scoring of molecular results and verification by alternative techniques) were not stated.

Statistical issues of importance for the compiled VUR studies include limitation to the details of analyses. In most studies it was also not possible to determine if multiple testing but restricted reporting was evident. Many studies reported results for a single DNA site analysis. Possibly a greater number of DNA sites were analyzed but only selected findings were reported. This selective reporting is not a new concept and had been raised elsewhere^{78,79}

TESTING FOR VUR

Being aware that a condition is genetic can facilitate detection in other family members before clinical presentation. Detection of a condition before disease occurrence is considered justified when early intervention improves outcomes for the patient⁸⁰. In siblings of children with primary VUR, justification for testing before clinical presentation, usually with a UTI, is not supported by strong evidence.⁸¹ Heightened parental awareness of the risk of UTI may be as beneficial as, and less harmful than, a VCUG.

For children 2 mo to 2 yr old who present with a first UTI, the American Academy of Pediatrics recommends ultrasonography and either voiding cystourethrography or radionuclide cystography.⁸² However, the strength of evidence supporting this guideline is acknowledged as only fair. Given the good prognosis for children with VUR and the absence of good evidence for improved outcomes, the invasive, unpleasant nature of a VCUG outweighs the possible benefit of prophylactic treatment. The importance of increased awareness of the parent and physician with respect to signs of a UTI should not be understated

Table 3. Studies that generate a hypothesis about association of specific genotype/protein type and phenotype that includes VUR but is not specifically VUR alone^a

Site Name and Acronym ^b	Chromosome Location	Association	Site/Mutation	N	Spectrum	Ref
Human leukocyte antigen/major histocompatibility complex, HLA	6p	No	HLA-A, -B, DR/DQ	48	PUJ/rUTI/bifid pelvis	149
Coagulation factor XIII, F13A1	6p25.3-24.3	No	1 RE site	32	PUJ/rUTI/bifid pelvis	149
GLI-Kruppel family member GLI3	7p13	No	All?	1	Pallister-Hall syndrome + VUR	150
Chromosome 8	8	Yes	Mosaic trisomy 8	1	Trisomy 8 syndrome + VUR	151
Chromosome 10	10	Yes	10p	1	UTI + VUR and pelvoureteric diverticulosis	152
	10	Yes	10p	1	Dev delay, congenital heart defect, multicystic kidneys, grade V VUR	153
	10	Yes	10q	10	Urinary anomalies, VUR, hypoplastic kidneys	154
Receptor tyrosine kinase, RET	10q11.2	No	cDNA + 4 markers	24	Medullary thyroid carcinoma, UTIs, atrophic kidney	155
Glial cell line-derived neurotrophic factor receptor alpha, GDRFA1	10q26	No	All for proband, markers for family	23	Medullary thyroid carcinoma + UTI, atrophic kidney	155
Paired-box gene 2, PAX2	10q26	Yes	All exons (c1104delC exon 5)	11	Optic nerve colobomas, renal anomalies and VUR	156
	10q26	Yes	All exons	18	Optic nerve colobomas + VUR	157
	10q26	Yes	Exon 2	6	Renal coloboma syndrome (VUR in 1 patient)	158
Chromosomal 13	13q33-34	Yes	D13S1311 to D13S285	2	VUR + renal failure/hydronephrosis + developmental delay	159
Glial cell line-derived neurotrophic factor, GDNF	15p13.1-12	No	2 Exons + 2 flanking markers	23	Medullary thyroid carcinoma + UTI, atrophic kidney	155
Prader Willi, PWCR	15q11-12	Yes	Del 15q11-12	1	PWS + VUR	160
Smith-Magenis syndrome, SMCR	17p11.2	Yes	17q del	1	SMS + grade IV VUR	33
Angiotensin-converting enzyme, ACE	17q29	No	Intron 16, del287bp	119	27 VUR (102 CAKUT)	161
Chromosome 22	22	Yes	22q11.2	5	22q deletion syndrome	162
Uroplakin IIIA, UPK3A	22q13.32	Yes	All exons	17	Aplasia/dysplasia, obstruction, posterior valves,	57
Angiotensin II type 2 receptor, AGTR2	Xq22-25	No	g-1332A>G, g1593C>A	119	27 VUR (102 CAKUT)	161
Linkage studies genome-wide	1-46	Yes, 1p	387 Markers, ≈10 cm apart	58 (7 families)	VUR, RN, urinary problems, VUR + RN	73
targeted genome sites	1p13, 3p12, 6p21, 10q26, 19q13	No	35 Microsatellite markers	49 (7 families)	VUR, ESRD, rUTI	163

^aStudies are ordered by chromosomal location. HLA, human leukocyte antigen/major histocompatibility complex; UTI, urinary tract infection; PWS, Prader Willi Syndrome; SMS, Smith-Magenis syndrome; ACE, angiotensin-converting enzyme; RE, restriction enzyme; RN, reflux nephropathy; rUTI, recurrent UTI.

^bHUGO nomenclature.

Table 4. Studies that test the hypothesis of an association between a genotype/protein type and the phenotype of VUR^a

Name and Acronym ^b	Chromosome Location	Association	Site/Mutation	N	Method	Spectrum	Reference
Nonsevere VUR roundabout, axon guidance homolog, ROBO2	3p12.3	Yes (2 of 124 families)	c3477T>C,c4349G>A	>800	Sequencing	Proband high-grade VUR + other abnormalities; familial, no details (124 families); control n = 552	164
human leukocyte antigen/ major histocompatibility complex, HLA	6p	Yes	HLA-DR11, DRB1*1101, DRB1*1502	533	PCR-sequence spec primers	VUR alone	165
angiotensin-converting enzyme, ACE	6p 6p 17q23	Yes Yes (AW32) No	Prot; HLA-A/B Prot; HLA-A/B Intron 16, del287bp	38 36 407	Serotyping Serotyping PCR + electrophoresis	Familial VUR UTI + VUR VUR alone	166 167 168
uroplakin IIIA, UPK3A	22q13.31	No	Intron 16 del287bp	162	PCR + electrophoresis, + insertion-specific PCR	VUR alone	169
G protein β 3 subunit, GNB3	12p13	Yes	Intron 16 del287bp	162	PCR + electrophoresis	Familial VUR	170
uroplakin IA, UPK1A	19q13.1	No	Intron 16 del287bp	157	PCR + electrophoresis	VUR (all grades)	171
		No	Intron 16 del287bp	125	PCR + electrophoresis	VUR alone	172
		No	Intron 16 del287bp	109	PCR + electrophoresis	VUR alone	173
		Yes	Intron 16 del287bp	78	PCR + electrophoresis	VUR alone	174
		Yes	P154A	393	Sequenced	VUR alone	175
		Yes	C825T	305	PCR-RFLP	VUR alone	176
		Yes	A7V	166	Sequenced	VUR alone	175
		No	S31A	166	Sequenced	VUR alone	175
		No	M255T	166	Sequenced	VUR alone	175
		No	R113Q	166	Sequenced	VUR alone	175
		No	Exons 3 and 5	166	Sequenced	VUR alone	175
		No	g1166A>C	125	PCR-RFLP	VUR alone	172
		No	g1166A>C	109	PCR-RFLP	VUR alone	173
		No	g1166A>C	42	PCR-RFLP	VUR alone, males only	177
		Yes	g-1332A>G	125	PCR-RFLP	VUR alone	172
		No	g3123A>C	109	PCR-RFLP	VUR alone	173
		No	g-1332A>G	42	PCR-induced RFLP	VUR alone, males only	177,178
		No	g-1332A>G (+ all exons)	427 (76)	PCR-RFLP (sequenced)	Familial VUR (VUR alone)	170
angiotensinogen, AGT	1q42-43	No	M235T	109	PCR-RFLP	VUR alone	173
paralemmin-like, PALML	1q21-22	No	All exons	52	SSCP + HD	Familial VUR	179
ABO blood group	9q34.1-34.2	Yes	Prot; ABO	36	Serotyping	rUTI (16 with VUR)	167
uroplakin 3B, UPK3B	7q11.2	No	All exons	25	Sequenced	VUR alone	180
paired-box gene 2, PAX2	10q26	No	Exons 2-5	23	SSCP	Familial VUR	181

Table 4. Continued

Name and Acronym ^b	Chromosome Location	Association	Site/Mutation	N	Method	Spectrum	Reference
Severe VUR human leukocyte antigen/ major histocompatibility complex, HLA	6p	Yes	Prot; HLA/B	570	Serotyping	RN-ESRD	182
Kallikrein promoter, KLK1	19q13.3	No	g-130G ₁₀ >G ₂ C ₇ >G ₁₁ >G ₁₂	244	SSCP + HD, allele-specific PCR	VUR>grade II, 19% with ESRD	183
angiotensin converting enzyme, ACE	17q23	No	Intron 16 del287bp + 5 other sites	191	PCR + electrophoresis (size analysis)	16 + ESRD, 58 VUR only	184
		No	Intron 16 del287bp	143	PCR + electrophoresis (size analysis), + insertion-specific PCR	VUR III-IV, no scars	185
		Yes	Prot, mRNA	11	Antibody + sections, ISH-oligo, RT-PCR	Severe + RN	186
angiotensin II type 1 receptor, AGTR1	3q21-26	No	7 sites	191	SSCP	16 + ESRD, 58 VUR only	184
angiotensinogen, AGT	1q42-43	No	7 sites	191	Electrophoresis, SSCP, PCR-RFLP	16 + ESRD, 58VUR only	184
TNF α	6p21.3	Yes	g-308G>A	134	PCR + electrophoresis (size analysis)	High-grade VUR + RN	187
TGF β 1		Yes	g-509C>T, g869T>C, g915G>C	123	RFLP	High-grade VUR + RN	188
prostaglandin-endoperoxide synthase 2, PTGS2	1q25.2-25.3	Yes	Prot	18	Immunohistochemistry, Wstrn, RT-PCR	VUR + RN	53
IGF1	12q22-23	Yes	Prot, mRNA	15	Histochemistry, ISH	RN	189
IGF1 receptor, IGF1R	15q26.3	Yes	Prot, mRNA	15	Histochemistry, ISH	RN	189
EGF	4q25	Yes	Prot, mRNA	15	Antib + sections, ISH-oligo	Severe + RN	190
monocyte chemotactic peptide-1, CCL2	17q11.2-21.1	Yes	Prot, mRNA	15	Antib + sections, ISH-oligo	Severe + RN	190

^aStudies are grouped by VUR spectrum (i.e., nonsevere VUR and severe VUR). Studies are ordered by sample size within the specific gene studied. Prot, protein; SSCP, single-stranded conformational polymorphism; HD, heteroduplex analysis; RFLP, restriction fragment length polymorphism; ISH, *in situ* hybridization; Wstrn, Western Blot (protein); Sthn, Southern blot; RT-PCR, reverse transcription PCR; Antib, antibody.

^bHUGO nomenclature.

because these may be helpful in directing diagnosis of an otherwise nonspecific illness and ensures prompt treatment.

PROGNOSIS

What is evident when the frequency of VUR is compared with that of end-stage kidney disease attributed to VUR is that the outcome for most children with VUR is excellent. Assume that VUR occurs in more children than the currently reported 1% to 2%: *e.g.*, if VUR occurs in 3% of children, or 30,000 per million children, then only 1 in 6000 children (or 5 per million children) will develop end-stage kidney disease (Figure 2). VUR is a relatively common abnormality and end-stage kidney failure is uncommon, especially caused by reflux nephropathy. Approximately 5% to 7% of people entering end-stage kidney failure programs have reflux nephropathy nominated as the primary cause.^{83–88} This is rarely a biopsy diagnosis but generally a clinical diagnosis based upon past history of renal tract imaging appearances.^{89–91} Factors other than VUR must be on the causal pathway to produce sufficient kidney damage to result in kidney failure. UTI is usually regarded as the culprit,

causing damage to the kidney and turning a refluxing normal kidney into a severely damaged one that ultimately fails. This also seems unlikely given that UTI is a common problem, occurring in about 6% of all children, because cohort studies suggest that damage exists before UTI¹⁹ and few new abnormalities arise after UTI.^{92,93} These data suggest that the key event in the causal pathway for severe renal parenchymal abnormality associated with VUR occurs antenatally as part of the reflux-congenital renal hypoplasia/dysplasia syndrome. There is a complex interplay between VUR, UTI, and renal parenchymal abnormality. Of the three, severity of renal parenchymal abnormality is the factor most predictive of long-term outcome, and the contribution of post-UTI renal parenchymal abnormality is likely to be small compared with the congenital abnormality.

MANAGEMENT

Few areas of nephrology are as controversial as the management of a child with suspected VUR. Historically, children with VUR were identified by routine VCUG after UTI, particularly in children under 5 yr of age. Justification was based on assumptions of adverse clinical outcomes if untreated and that treatment improved outcomes. Evidence of benefit for treating VUR is inadequate. Two trials of 247 children have demonstrated no significant difference in risk of UTI, or in renal parenchymal abnormality, between children randomized to low-dose antibiotic and those randomized to surveillance/no treatment (Figure 3).^{94,95} Six trials have compared open surgical ureteric reimplantation plus antibiotic prophylaxis with antibiotic prophylaxis alone, and two trials have compared subureteric injection plus antibiotics with antibiotics alone. Combining these studies demonstrates that risk of UTI at 1 to 2 and 5 yr and new or progressive renal parenchymal abnormality at 5 yr is not significantly different between the surgical/antibiotic groups compared with antibiotics alone. The only difference was a lower risk of febrile UTI in the surgical/

antibiotic group such that about 15 children would need to be re-implanted to prevent one febrile UTI over 5 yr. Given that this outcome was unblinded and no difference in upper tract outcomes was shown, this result is probably an overestimate of effect. In 2006, 10-yr follow-up data on 252 of an original group of 306 trial participants were published.⁹⁶ These data showed that renal growth, UTI recurrence, somatic growth, and renal function did not differ between the surgery plus antibiotic and antibiotic alone groups. The only difference was a greater number of febrile infections in the antibiotic group (Figure 4). Two trials have compared different subureteral injection substances, and numerous treated-case series exist.⁹⁷ Common to most of these studies is absence of clinically relevant outcomes such as symptomatic urinary tract infection, hypertension, and long-term renal function. Case series suggest subureteral injection frequently resolves the physical abnormality that is VUR, but the effect on occurrence of UTI and renal outcomes is not known. In summary, the trial data that supports the use of prophylactic antibiotics, reimplantation surgery, and subureteral injection to prevent recurrent UTI in children with VUR is weak and inconclusive.

Not surprisingly then, the practice of detecting VUR using VCUG after UTI has been questioned, with many suggesting that the practice should be abandoned^{93,98–102} Currently there is no evidence that interventions for children with VUR confer benefit, but neither is there evidence from randomized trials that interventions are not beneficial. We are currently in an evidence-poor environment, trading off possible benefits against probable harms. In such a setting, clinical practice is likely to vary on the basis of clinician choice and the values of parents of children with suspected VUR.

FURTHER STUDIES

Randomized controlled trials are needed to determine whether prophylactic antibiotics prevent recurrent UTI in children with VUR. Perhaps

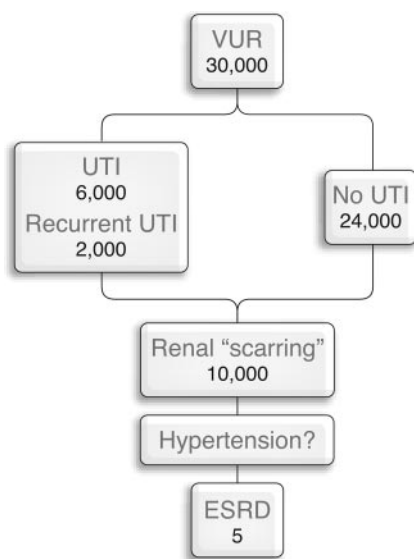
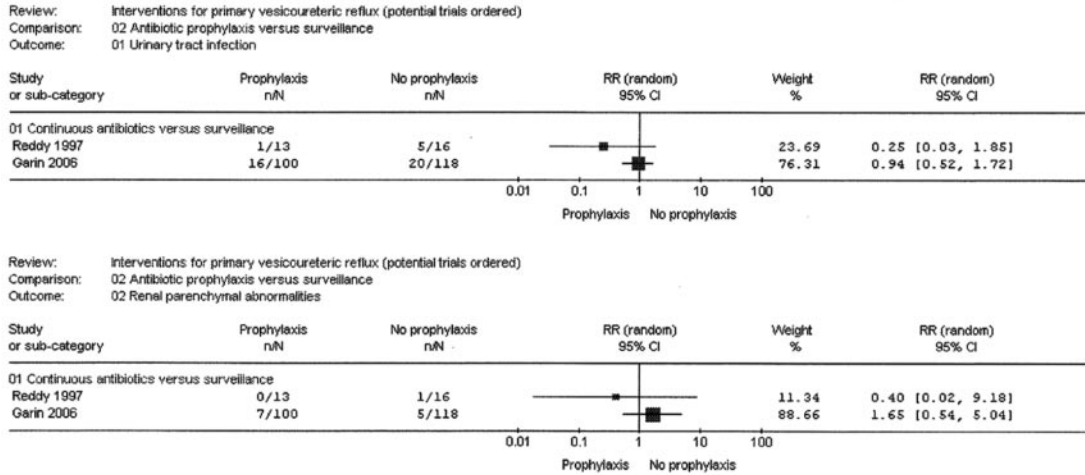


Figure 2. Natural history of vesicoureteral reflux, from a population of 1,000,000 children (assuming a prevalence of VUR of 3%).¹³



Surgery (re-implantation or subureteral injection) plus antibiotics vs antibiotics alone

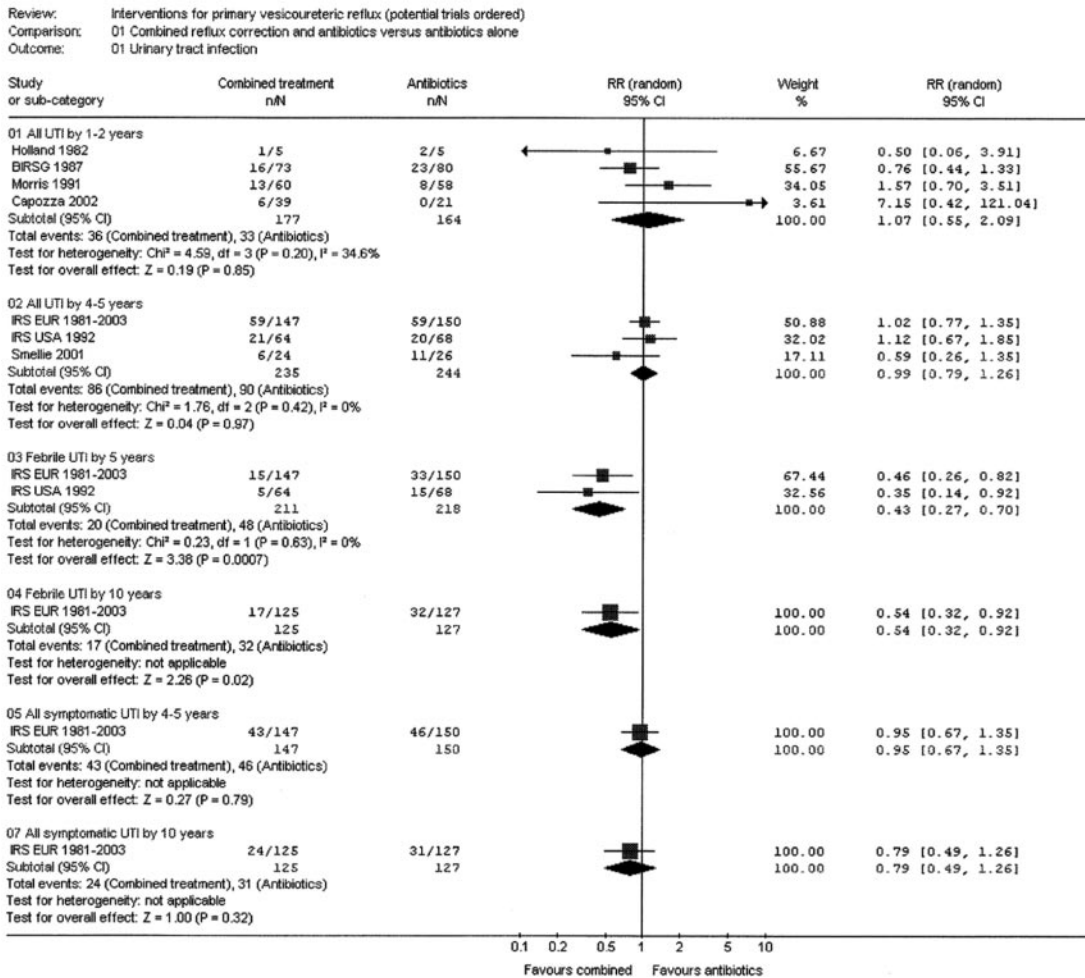


Figure 3. Meta-analysis of randomized controlled trials of antibiotics versus no treatment/surveillance for the outcome of urinary tract infection.⁹⁸

more importantly, genetic epidemiological studies are needed on the rare group of children with VUR and clinically

important renal parenchymal abnormality to better define the causal pathway and identify potentially mod-

ifiable environmental factors. A United Kingdom initiative has commenced collection of DNA samples from sib-

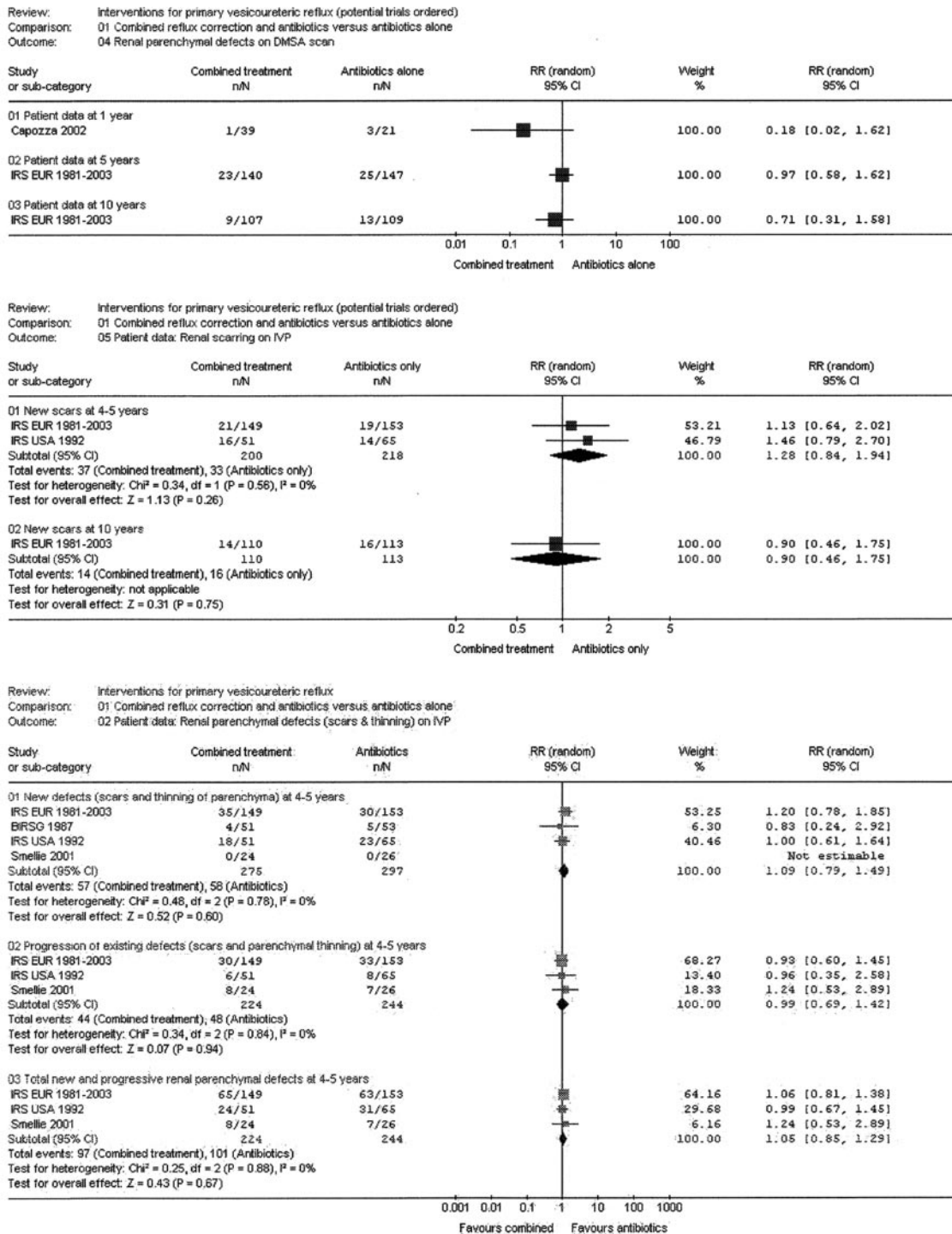


Figure 4. Meta-analysis of randomized controlled trials of reimplantation surgery plus antibiotics versus antibiotics alone for the outcome of renal parenchymal abnormality.⁹⁸

ling pairs with VUR (<http://www.vu-r.org.uk>). Details on the diagnostic criteria or detail of phenotypic syndrome are not provided on the web site. Hopefully, sufficient information is re-

corded to allow targeting of the severe spectrum of VUR. Ideally, environmental factors covering the pre- and postnatal periods will also be recorded. Development of a consensus statement

about reporting practices for genetic association studies would be a step toward more complete reporting of these types of studies and subsequent better compilation of evidence.

DISCLOSURES

None.

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